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Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 28-83 are pending in the application, with claims 28, 46, and 66 being the independent claims. Claims 1-27 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 28-83 are sought to be added. Support for this amendment can be throughout the specification, for example, on pages 2-3, paragraphs [0005]-[0006]; page 6, paragraph [0024]; page 7, paragraphs [0025] and [0026]; page 8, paragraphs [0031]-[0034]; page 9, paragraph [0036]; page 12, [0049]; and in the Examples, beginning on page 17, paragraph [0064]; specifically Example 1, page 20, paragraph [0068]; Example 2, page 21, paragraph [0070]; Example 5, page 24, paragraph [0076]; and Example 8, page 27, paragraph [0082]; and Figure 4. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 1, 3, and 4 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Nasmyth *et al.* Specifically, the Examiner alleged that Nasmyth *et al.* discloses a method to identify substances to interfere with APC and includes all the

components of the present invention. Applicants respectfully traverse this rejection as it may apply to the amended claims.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."

Verdegaal Bros. V. Union Oil Co. of California, 814 F.2d 628, 613, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claims 28-65 are drawn to methods for screening for substances that inhibit the ubiquitination reaction mediated by APC11 in the absence of other APC subunits. Nasmyth *et al.* discloses the use of the APC holoenzyme or subsets thereof for screening for inhibitors of progression into anaphase, whereas the method of the present invention is a screen for inhibitors of APC-mediated ubiquitination. Nasmyth *et al.* specifically states that APC1, APC2, APC4, and APC5 are *required* for APC function of the disclosed assay and provides data showing yeast cells knocked out in these genes as being significantly delayed in anaphase onset (*see* Examples 7 and 10). As shown in Examples 1, 2 and 5, the proteins encoded by these genes are not required in the claimed method for screening inhibitors of APC11-mediated ubiquitination. Therefore, Nasmyth *et al.* clearly does not teach each and every element of the claims as amended.

The method of independent claim 66 and its dependents 67-83 is a screen for inhibitors of APC11 self-ubiquitination. The screening method of these claims does not use additional APC substrate. Nasmyth *et al.* specifically states that a substrate is a part of the reaction, as on page 7, "[t]he screening methods of the invention are based on the principle to determine the ability of the APC to ubiquitinate a cyclin B containing substrate." Further, Nasmyth *et al.* continues to require a substrate in every description

of the assay, as on page 7, paragraph 5, page 8, first full paragraph, and throughout the Examples. Nowhere does Nasmyth *et al.* describe APC11 self-ubiquitination. Therefore, Nasmyth *et al.* does not disclose the method of screening for inhibitors of APC11 self-ubiquitination and cannot anticipate the claims.

Because each and every element of the claims is not taught, Nasmyth *et al.* cannot anticipate the present claimed invention under 35 U.S.C. § 102(b). Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-27 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nasmyth *et al.*, in view of Kirschner *et al.*, and further in view of Hatfield *et al.* and Gonen *et al.* Specifically, the Examiner alleged that Nasmyth *et al.* discloses a “screening method involving the incubation of APC11 as the E3 enzyme, E1 enzyme, and E2 enzyme, ATP and a substrate (cyclin B)...” Further, the Examiner alleged that Kirschner also discloses a screening method for inhibitors of “ubiquitination events involving a subunit of APC (E3), and E1 enzyme, E2 enzyme, ubiquitin, ATP, and a substrate...”. The Examiner further alleged that Hatfield *et al.* and Gonen *et al.* disclose UBA1 and UBCH5b, respectively. The Examiner alleged that a person of ordinary skill in the art would be motivated to combine the references and such a combination would result in the screening method of the present invention. Applicants respectfully traverse this rejection as it may be applied to the amended claims.

New claims 28-65 are drawn to methods for screening for substances that inhibit the ubiquitination reaction mediated by APC11 in the absence of other APC subunits.

Claims 66-83 are drawn to a method of identifying inhibitors of APC11 self-ubiquitination. *In re Vaeck* (947F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)), outlines the factors required for establishing a *prima facie* case for obviousness: prior art references that teach all claim limitations, a motivation to combine the references in the references themselves or knowledge known to a person of skill in the art at the time the invention was made, and a reasonable expectation of success from the combination elements in the references. As discussed below, Applicants respectfully assert that these requirements have not been met to support a *prima facie* argument for obviousness for the amended claims.

The cited references do not contain every limitation of the claims.

Nasmyth *et al.*, as discussed *supra*, discloses the use of the APC holoenzyme or subsets thereof for screening for inhibitors of progression into anaphase. Nasmyth *et al.* also discloses that APC1, APC2, APC4, and APC5 are required for their assay and provide no guidance regarding the ubiquitination of APC11. As stated before, this reference does not teach every limitation of the claims as amended.

The supporting documents cannot remedy the deficiencies of Nasmyth *et al.* Kirschner *et al.* discloses a “mitotic destruction complex” including CDC27 and CDC16, with no mention of APC11, for ubiquitinating substrates (*see* Kirschner *et al.*, page 4, lines 31-35). Hatfield *et al.* discloses the characterization of an E1 protein, but not the activity of APC. Gronen *et al.* discloses the function of E2s in the destruction of IκBα. Clearly, none of the supporting references disclose the use of APC11 in the absence of other APC subunits with ubiquitin, an APC substrate and a test compound to screen for

substances that inhibit the ubiquitination of APC substrates by APC11 or APC11 self-ubiquitination. Therefore, the combination of references cited by the Examiner cannot teach every limitation of the claims as amended.

There is no motivation to combine the cited references.

A person of skill in the art would have no motivation to combine the cited references as none of the references contain any suggestion to do so. The data in each reference was generated in different organisms and with different enzyme complexes and no suggestion was made to substitute the elements from the other systems. A person of skill in the art of APC would not necessarily look at the field of NF- κ B to look for alternative components. The cited references provide no motivation to do so.

There is no expectation of success.

A person of skill in the art would have no expectation of successfully developing the claimed method of the present invention by combining the references cited by the Examiner. The ability of APC11 to ubiquitinate in the absence of other APC subunits and self-ubiquitinate in the absence of other APC subunits as in Example 1 of the specification was surprising. As discussed *supra*, the cited references either do not mention APC or state that additional subunits are required for the ubiquitination process. Therefore, there can be no expectation of success for combining the cited references to generate the claimed invention.

For the reasons stated above, Applicants believe that a *prima facie* case for obviousness has not been established for the claims as amended. Applicants therefore respectfully request that the rejection be withdrawn.

Foreign Priority

Applicants respectfully request that the Examiner acknowledge receipt of the certified copy of priority document EP 00113832.0 which was filed with the application on July 29, 2001.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
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- 18 -

Gmachl *et al.*
Appl. No. 09/893,443

Version with markings to show changes made

Claims 1-27 were cancelled

Claims 28-83 were added.

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